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SUGHRUE MION ZINN
MACPEAK & SEAS PLLC
2100 PENNSYLVANIA AVENUE NW
WASHINGTON DC 20037-3202

EXAMINER
WILDER,C

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Please find below and/or attached an Office communication concerning this application or proceeding.

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1- File Copy

Office Action Summary	Application No. 09/345,761	Applicant(s) Ishiguro, T et al.
	Examiner CB Wilder	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 26, 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *30-50* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *30-50* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *10*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on March 26, 2001 in Paper No. 18 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/345, 761 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Objections

2. The claims 30-50 are objected to because the lines are crowded too closely together, making reading and entry of amendments difficult. Substitute claims with lines one and one-half or double spaced on good quality paper are required. See 37 CFR 1.52(b).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

4. Claims 30-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claim 30-50 lack proper antecedent basis in claim 30, step (2) for "first sequence" because the prior step or preamble do not recite "a first sequence". It is suggested amending the claim such that the claim language agree.

(b) Claims 30-50 are indefinite and confusing at step (2) for "a reagent (A) which allows the single stranded RNA to be cut" and at step (3) because it is unclear if reagent (A) actually cuts the single-stranded RNA or if the feature of "cutting" is only a property of the reagent (A) or if some other reagent is responsible for the cutting of the single-stranded RNA. Additionally, it is also suggested identifying reagent (A) in claim 30 for clarity as recited for reagents (B)- (J).

(c) Claim 30-50 are indefinite and confusing at "exposing" in claim 30 (step (2)) because the term "expose" do not recite an active, positive method step and it is unclear how the claimed step operates to "expose" the first sequence to the reagent (A).

(d) Claims 30-50 are confusing overall because it is unclear how reagent (A) operates to cut a single-stranded RNA when reagent (A) is a single-stranded oligo nucleic acid or when reagent (A) is a DNA or when reagent (A) is a DNA enzyme as recited in claims 31, 32, 35 and 49. Additionally, a DNA would not be expected to "cut" a single-stranded RNA molecule. Clarification is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 30, 32-40, 44 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. (Davey, herein) (5,409,818, filing date June 24, 1988) in view of Olson et al. (Olson, herein) (WO 91/04340, April 4, 1991). The rejections are based on the examiner's best understanding of the claimed invention because the claim language is confusing. Regarding claims 30 and 44, Davey et al. (5,409,818, April 1995) teach a method for assay a single-stranded target RNA molecule at a relatively constant temperature and without serial additions of reagents but in functional combination, or all at once, comprising the steps of (A) providing a single reaction medium containing reagents comprising: (i) a first oligonucleotide primer, (ii) a second oligonucleotide primer comprising an antisence sequence of an RNA polymerase promoter, (iii) a DNA-directed RNA polymerase that recognizes said promoter, (iv) an RNA-directed DNA polymerase, (v) a DNA-directed DNA polymerase, (vi) ribonucleoside and deoxyribonucleoside triphosphates; then (b) providing in said reaction medium RNA comprising an RNA comprising an RNA first template which comprises said specific nucleic acid sequence or a sequence complementary to said specific nucleic acid sequence, under conditions such that a cycle ensues wherein (1) said first oligonucleotide primer hybridizes to said RNA first template, (ii) said RNA-directed DNA polymerase uses said RNA first

template to synthesize a DNA second template by extension of said first oligonucleotide primer and thereby forms an RNA-DNA hybrid intermediate, (iii) said ribonuclease hydrolyzes RNA which comprises said RNA-DNA hybrid intermediate (iv) said second oligonucleotide primer hybridizes to said DNA second template, (v) said DNA-directed DNA polymerase uses said second oligonucleotide primer as template to synthesize a functional RNA polymerase promoter by extension of said DNA second template and (vi) said DNA-directed RNA polymerase recognizes said functional promoter and transcribes said DNA second template, thereby providing copies of said RNA first template; and thereafter (c) maintaining said conditions for time sufficient to achieve a desired amplification of said specific nucleic acid sequence (column 5, lines 26-68 and column 6, lines 1-6). Davey further teach a probe labeled with a fluorophore (col. 9, lines 5-7 and 34-36) and an additional step of detecting or quantifying the single-stranded RNA in the sample based on the measured fluorescent signal or change in the measured fluorescent signal (column 8, lines 54-65). Davey teaches that is assay method is advantageous because it requires less participation and fewer manipulation by the user.

The single-stranded RNA assay method of Davey differs from the claimed invention in that Davey does not teach a reagent (A) which allows the single-stranded RNA to be cut at the 5' end of the specific nucleic acid sequence nor does the reference teach wherein the oligonucleotide containing the promoter sequence includes an enhancer sequence for the promoter. The Examiner however takes notice that enhancer sequences were routinely used in the prior art with promoter sequences to increase the level of transcription. In a method similar to that of Davey et al. for assaying a target nucleic acid (DNA or RNA of interest). In a method similar to that of Davey et al. for assaying

target DNA or RNA of interest, Olson teaches wherein the target nucleic acid is exposed to a reagent which allows the target nucleic acid to be cut at the 5' end of the specific nucleic acid sequence and wherein the product from the cutting step is hybridized to a primer complementary to a sequence at the 3' end of the specific nucleic acid sequence (page 5, beginning at line 16 to page 6, line 33). Olson et al. further teach that the target sequence is cut to isolate the region of interest having a defined 3' end available for hybridization (page 5, lines 27-33 and page 22, lines 21-33). In view of the foregoing, it would have been obvious to one of ordinary skill in the art to have been motivated to incorporate an agent which cuts the target nucleic acid at selected sites as taught by Olson in the method of assaying for a target nucleic acid as taught by Davey for the benefit of producing a specific target nucleic acid at a selected site for analysis by hybridization and amplification as suggested by Olson.

Regarding claim 32, Davey et al. teach wherein a reagent which is DNA is added to the method and wherein the method further comprises a step of adding RNAase H and a subsequent step of deactivating the RNAase H by heating or by the addition of an inhibitor prior to addition of the reagent (b) (column 6, line 19 and column 8, lines 20-33).

Regarding claims 33 and 34, Davey et al teach wherein the reagents are added sequentially and simultaneous (column 8, lines 35-37 and lines 54-62).

Regarding Claim 35, Olson et al. teach wherein the reagent (A) which allow cutting a target nucleic acid is a DNA enzyme or non-enzymatic compound (page 21, 24-33 and page 22, lines 1-33). The Examiner takes notice that ribozymes were routinely used in the prior art as a

catalyst in methods for assaying RNA. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art to include a ribozyme as a first reagent in the method for assaying RNA for convenience of specifically cleaving RNA molecules of interest as well known in the art.

Regarding claim 36, Davey teaches wherein the enzyme which degrades RNA in a DNA-RNA double strand is the RNA-dependent DNA polymerase reagent (column 5, lines 26-35).

Regarding claim 37, Davey teaches wherein an enzyme having both an RNA-dependent DNA polymerase activity and a DNA-dependent DNA polymerase activity is used as two separate reagents (column 7, lines 48-68 and column 8, lines 1-19).

Regarding claim 38, Davey teaches wherein the enzyme is avian myoblastome virus polymerase (column 7, lines 53-55).

Regarding claim 39, Davey teaches wherein two reagent in the method identified as reagents (b) and (F) are used at concentrations of from 0.02 to 1 micro molar (column 17, example 8, line 35).

Regarding claim 40, Davey teaches wherein the DNA-dependent RNA polymerase as the reagent (H) is either phage SP6 polymerase, phage T3 polymerase or the phage T7 polymerase (column 7, lines 38-41).

Regarding claim 50, Davey discloses utilizing relatively constant temperature for the amplification process of about 42 degrees Celsius (examples 3-9 columns 15-17).

The order of combination of method steps as described in claims 30-40, 44, and 50 are not critical to the claimed invention. *In re Burhans*, 69 USPQ 330 states that a selection of any order of performing process steps is **prima facie** obvious in the absent of new or unexpected results.

7. Claims 41-43 rejected under 35 U.S.C. 103(a) as being unpatentable over Davey as described above, in view of Ishiguro et al. (Ishiguro, herein) (6,063,572 filing date January 23, 1998).Regarding claims 41-43, Davey in view of Olson teach a method of assaying a specific nucleic acid sequence using an amplification process as discussed earlier. The method of Davey in view of Olson et al. differs from the claim invention in that the references do wherein the not teach using an intercalative fluorescent dye as one of the reagents involved in fluorescent labeling. Ishiguro teaches a method of assaying a specific nucleic acid comprising: (a) adding to a sample an oligonucleotide primer, wherein the nucleotide sequence of the primer is complementary to the target nucleic acid sequence and comprises a RNA polymerase promoter sequence, wherein a duplex is formed between the target nucleic acid and the primer when the target sequence is present in the sample; (b) elongating the primer in a duplex with the target nucleic acid sequence in (a) to produce a double-stranded polynucleotide; (c) reacting the double- stranded polynucleotide produced in (b) with RNA polymerase to produce RNA (d) adding an oligonucleotide probe complementary to the RNA in (c) wherein the probe is labeled with a fluorescent intercalative dye; (e) measuring the fluorescence of the intercalative dye (see claim 1 and abstract). Ishiguro teaches that the fluorescent intercalative dye as the label may be linked to any site of the nucleotide, including the 5' end, the 3'-end and the center,

as long as the linkage neither hinders the fluorescent intercalative dye from intercalating to double-stranded DNA nor hinders the oligonucleotide from hybridizing with the RNA (col. 5, lines 54-59). Ishiguro teaches that the intercalative dye-labeled probe coexisting in the reaction solution enhances the fluorescent intensity in proportion to the amount of hybrid which makes it possible to detect the specific nucleic acid or determine the initial amount of the specific nucleic acid by measuring the fluorescent intensity of the reaction before and after, or during the detection step (col. 6, lines 44-51). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have been motivated to modified the method of assaying a target nucleic acid as taught Davey in view of Olson with the an intercalative fluorescent dye linked an oligo-DNA as taught in the method of assay a specific nucleic acid of Ishiguro. One of ordinary skill in the art would have been motivated to do so for the benefits taught by Ishiguro that an intercalative dye-labeled probe coexisting in a reaction solution enhances the fluorescent intensity in proportion to the amount of hybrid which makes it possible to detect a specific nucleic acid or determine the initial amount of a specific nucleic acid by measuring the fluorescent intensity of the reaction before and after, or during the detection step (col. 6, lines 44-51).

8. Claims 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davey in view of Olson and further in view of Newton (PCR, Essential Data, 1995). Regarding claim 45, Davey in view of Olson teach a method of assaying a specific nucleic acid using an amplification process as described earlier. The claimed invention differs from the references in that they do not teach wherein all the reagents are chloride-free. In a guide for PCR, Newton discloses an amplification reaction

buffer, wherein all the reagents are chloride-free (page 149, table 1, buffer #2). Newton further teaches an advantage of a chloride-free buffer is evident in the fact that some enzymes perform better in a PCR buffer than in their standard recommended buffer (page 144, column 1, second paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have been motivated to modify the reagents in the method of assaying a target nucleic acid at taught by Davey in view of Olson with the chloride-free reaction buffer of Newton for the expected benefits of maximizing enzyme activity based on Newton's teaching that some enzymes perform better in a PCR buffer than in their standard recommend buffer (page 144, column 1, second paragraph).

Regarding claim 46, Newton teaches wherein acetate in used in the amplification reaction (page 149, table 1, buffer #2).

Regarding claim 47, Newton teaches using magnesium acetate at a concentration of 10 mM and using potassium acetate at a concentration of 66 mM (page 149, table 1, buffer #2).

9. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davey in view of Olson et al. and further in view of Cleuziat et al. (Cleuziat, herein) (5,824,517 filing date May 16, 1997). Davey in view of Olson teach a method of assaying a specific nucleic acid sequence using an amplification process as discussed earlier. The method of Davey in view of Olson differ from the claimed invention in that the references do not teach wherein sorbitol is added to the reaction. In a method similar to the method of Davey, Cleuziat discloses using an amplification reaction to assay nucleic acid sequences. Cleuziat further teaches wherein polyols such as sorbitol can be used in a reaction mixture to aid in accomplishing amplification. Cleuziat teach that such a reagent along with

denaturing agents and stabilizing agents are useful for reducing non-specific hybridization reactions that could generate background noise (col. 9, lines 11-19). In view of the foregoing, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate sorbitol as taught by Cleuziat in the method of assaying a target nucleic acid as taught by Davey in view of Olson for the expected benefit of accomplishing amplification with a reduction in non-specific hybridization and background noise as suggested by Cleuziat.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Examiner Cynthia Wilder whose telephone number is (703) 305-1680. The Examiner can normally be reached on Monday through Thursday from 7:00 am to 5:30 pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Exr.'s supervisor, W. Gary Jones, can be reached at (703) 308-1152. The official fax phone number for the Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed the Group's receptionist whose telephone number is (703) 308-0196.

Art Unit: 1655

Cynthia B. Wilder

Cynthia B. Wilder, Ph.D.

May 16, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

5/18/01